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## Human-Specific NOTCH2NL Genes Affect Notch Signaling and Cortical Neurogenesis.

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### Public Summary:

Genetic changes causing brain size expansion in human evolution have remained elusive. Notch signaling is essential for radial glia stem cell proliferation and is a determinant of neuronal number in the mammalian cortex. We find that three paralogs of human-specific NOTCH2NL are highly expressed in radial glia. Functional analysis reveals that different alleles of NOTCH2NL have varying potencies to enhance Notch signaling by interacting directly with NOTCH receptors. Consistent with a role in Notch signaling, NOTCH2NL ectopic expression delays differentiation of neuronal progenitors, while deletion accelerates differentiation into cortical neurons. Furthermore, NOTCH2NL genes provide the breakpoints in 1q21.1 distal deletion/duplication syndrome, where duplications are associated with macrocephaly and autism and deletions with microcephaly and schizophrenia. Thus, the emergence of human-specific NOTCH2NL genes may have contributed to the rapid evolution of the larger human neocortex, accompanied by loss of genomic stability at the 1q21.1 locus and resulting recurrent neurodevelopmental disorders.

### Scientific Abstract:

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